Treatment-induced brain plasticity in borderline personality disorder: review of functional MRI studies

Treatment-induced Brain Plasticity in Borderline Personality Disorder: review of fMRI studies

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Abstract

Whilst neural substrates of symptoms expression in Borderline Personality Disorder (BPD) have been studied extensively, neural mechanisms mediating post treatment amelioration of symptoms remain poorly characterized. Herein present review sheds a critical light on all here-to-date fMRI findings of brain changes in BPD patients following a treatment with psychotherapy or drugs. Preliminary evidence points to downregulation of neuronal activity within the insula and amygdala, together with differential employment of prefrontal areas, mainly orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dlPFC), as well as enhanced functional connectivity between limbic and prefrontal regions induced by DBT. Identifying neural circuits behind treatment processes may refine strategies to target specific symptoms, thereby resolving some of the controversies over BPD treatment.

KEYWORDS:

functional magnetic resonance imaging; borderline personality disorder; psychotherapeutic treatment; pharmacotherapy; treatment; therap

Introduction

Beyond delineating biomarkers of psychiatric disorders, novel neuroimaging techniques are used to provide neural parameters of therapeutic change, by measuring brain changes induced by specific modes of therapy. Understanding how various treatments achieve their therapeutic effects on the level of cerebral reorganization of specific circuits holds promise for more refined approaches to target more specific neuropathology.

Neuroimaging literature has recently begun to address neural mechanisms driving cerebral reorganization of specific circuits linked to post treatment amelioration of symptoms in patients with Borderline Personality Disorder (BPD). This severe psychiatric disorder is characterized by a pervasive pattern of instability in affect regulation, impulse control, self-image, cognition and interpersonal relationships [1]. The severity and morbidity of the disorder is associated with frequent self-damaging and impulsive behaviors, such as suicide, self-harm, or substance abuse [2,3]. Factor analysis and neurobiological studies have organized BPD symptoms around three domains of dysfunction, namely affective dysregulation, behavioural dysregulation (impulsivity) and disturbed relatedness [4]. While disturbance in interpersonal relations is characteristic of disordered personality in general, 'disturbed relatedness' was proposed to best describe the interpersonal style in BPD, uniquely characterized by turbulence and excessive fear of abandonment, presumably resulting from impaired mentalization capabilities and marked rejection sensitivity [5]. Since core domains of pathology are expressed to varying degrees in every patient and the diagnosis requires five out of nine criteria, the population of BPD patients results in abundant clinical variability. This contributes to the existing controversy over the treatment of BPD in terms of assigning patients on the basis of the diagnosis to one from a list of treatments that have shown superiority over treatment as usual [6,7]. Thus, identifying neural mechanisms behind treatment processes may tap into the patient heterogeneity disguised by the BPD diagnosis, and lead to a greater sophistication in matching of patients to specific interventions.

1) The Biological Basis of Borderline Personality Disorder

In neural terms the complexity of BPD is best understood as subtle deficits in multiple networks. Disturbances in the processing and regulation of emotions, characterized by aberrant variability in affective states and frequent negative emotions in response to seemingly neutral stimuli [for a review see ref. 8] are believed to constitute the core of borderline pathology [9, 2005p.372]. Studies probing emotional and cognitive processing in BPD have identified abnormal top-down processes,

characterized by dampened activity in prefrontal cortex (PFC) coupled with abnormal bottom- up emotion generation reflected in enhanced activity within limbic structures [for a review see ref. 10].

Growing body of neuroimaging data have highlighted hyperactivity in the amygdala [11-13] and insula [13] in the context of emotional stimuli, together with reduced activity in the ACC, OFC and frontopolar cortex (FPC). These findings led to assumptions of diminished recruitment of frontal brain regions involved in regulatory and inhibitory processes over enhanced limbic activity in emotional contexts [14, 15]. Whilst feelings of emptiness, dissociation, identity and interpersonal disturbances were found to be directly related to affective instability [16], self-injury is hypothesized to represent efficient, yet highly dysfunctional attempt to regulate disturbed emotions [17] based on deactivation of the amygdala [10] and lower posterior cingulate cortex (PCC) connectivity with the dlPFC by experimentally induced pain in BPD [18]. Moreover, impaired affect regulation may translate into perception bias while appraising social stimuli and thus contribute to difficulties in interpersonal functioning [see ref. 19 for a review, 20].

Studies of impulsivity in BPD involve scanning patients during holding or suppression of an already selected or initiated response and thus late control processes [21]. Stop-signal and Go/NoGo paradigms are the main behavioural inhibition tasks used to probe clinically salient interaction of negative affective processing and inhibitory control [22, 23]. Deficits in the recruitment of specific frontolimbic neural substrates providing control or 'brakes' for excessive bottom-up activity within limbic regions in the presence of negative emotional stimuli [24] and stress [25] have been identified. While healthy subjects selectively activated the posterior-medial OFC, dorsal ACC, dlPFC, amygdala and hippocampus in inhibitory control, BPD patients exhibited dysfunction in the posterior-medial OFC and the dorsal and subgenual ACC. Silbersweig *et al*. [13] provided further support for the model of impaired prefrontal inhibitory function in BPD patients in the context of negative emotions during a task requiring motor inhibition. Reported decreased activity in ventromedial PFC (including medial OFC and subgenual ACC), and elevated extended amygdalar ventral striatal activity was found to correlate with decreased constraint and increased negative emotion, respectively.

Functional neuroimaging of social cognition has started to elucidate possible cerebral substrates of emotional and behavioural facets in BPD contributing to impaired functioning in interpersonal context. 'Interpersonal hypersensitivity' have been proposed as the most prominent characteristic exacerbating interpersonal disturbances in BPD. It is associated with perceptions of others selectively biased toward negative emotions and attributes evidenced in the tendency to ascribe anger to ambiguous expressions (for a review see ref. 19), and to perceive others' faces as untrustworthy, relative to healthy controls [26]. Neuroimaging data have identified increased and prolonged amygdala responses [27, 28], and elevated activity in the anterior insula [29, 30] as neural substrates of interpersonal hypersensitivity, which led to assumptions of enhanced bottom-up emotion

generation processes [31]. The silence network which gives a stimulus the capacity to be favoured in early bottom-up evaluation processes for valence and salience appears to be mediated by functional coupling between the ACC and the amygdala, together with the anterior insula [32].

Since appraisal of others as threatening, deceitful and untrustworthy is likely to lead to poor social reward experience, alterations in mesolimbic circuitry have been proposed as the disturbed circuitry contributing to difficulties in interpersonal functioning in BPD. In particular, affected individuals are highly sensitive to threat of social rejection, negative judgement, unfairness, and exhibit general mistrust of others [26, 33- 38]. Indeed, mistrust and deficient cooperation constitute the core of borderline pathology, and are believed to reflect an insecure attachment style [39]. Furthermore, rejection sensitivity was found to mediate bias toward untrustworthy attributes of others and borderline traits [26, 37]. In neural terms, alterations in brain reward system activation including the pregenual ACC, ventral tegmental area and ventral striatum in response to social stimuli have been identified [40]. These results were interpreted as an evidence for a deficit in differentiation between reward and non-reward anticipation. In addition, trust game revealed that cooperation in BPD patients tended to decrease over time, presumably due to difficulties in perceiving the violation of social norms [36]. While healthy controls exhibited activation of the insula depending on the fairness of the transaction, in BPD individuals it was hyperactive during the whole experiment. Given that insula plays an important role in the processing of social stimuli and detection of unfairness [41], its hyperactivity in individuals with BPD may account for some of the difficulties in social interactions.

Deficit in mentalization, that is inability to represent one's own and other people's mental states is consistently reported in affective theory of mind/cognitive empathy tasks [see ref. 42, 43 for a review], and seems to be mediated by overactive or poorly regulated amygdala. Neuroimaging data have highlighted reduced activity in the superior temporal gyrus and sulcus during cognitive empathy task, as well as elevated activation of amygdala and somatosensory cortex during affective empathy in BPD patients relative to healthy controls [44-46].

The frontolimbic deficit was echoed in a recent meta- analysis, which highlighted elevated activity in amygdala-hippocampal and posterior cingulate cortex, and decreased bilateral dlPFC activation in response to negative versus neutral stimuli in BPD patients relative to healthy participants [47]. Moreover, the interplay between dlPFC and hippocampus was found to be deeply involved emotional and behavioural control in BPD [14, 15, 48, 49]. Interestingly, prior meta-analysis on neural correlates of emotion dysregulation yielded similar results, however, limbic hyperactivity was only seen in unmedicated patients, which demonstrates that sample characteristics may account for inconsistencies in findings [50].

2) What works in BPD treatment

Once deemed untreatable, today BPD patients have a more optimistic outlook on treatment with various psychotherapies and drug interventions. The gold standard of care recommends psychotherapy integrated with pharmacotherapy, wherein each modality targets specific domains of pathology [51]. The combined treatment approach has embraced the distinction between temperament and character proposed by the psychobiological model of personality disorders [52], which continuous to inform effective treatment planning. It identifies four dimensions which make up the temperament construct, namely novelty seeking, harm avoidance, reward dependence and persistence; and three dimensions of character including self- transcendence, self- directedness, and cooperativeness. Whilst temperament manifests itself early in life, tends to be highly stable over time, and is deemed responsive to pharmacotherapy, the latter is malleable, develops throughout adulthood, and is therefore amenable to treatment with psychotherapy. In this view, a patient manifesting impulsivity and affect dysregulation is a candidate for a treatment with medications, such as the selective serotonin re-uptake inhibitors (SSRIs), whereas low scores in self- directedness and cooperativeness for instance, are targeted with an appropriate psychotherapy.

2.1) Psychosocial treatments for BPD

Variety of psychotherapeutic approaches have been designed specifically for BPD, and five established as evidence based treatment, namely Dialectic Behavioral therapy (DBT), Mentalization-Based treatment (MBT), Transference- Focus psychotherapy (TFP), Schema- Focused therapy (SFT) and systems training for emotional predictability and problem solving (STEPPS) [53]. DBT and MBT are the most researched, refined and widely adopted approaches with the largest evidence base for BPD treatment [54-58].

DBT was developed for suicidal patients based on BPD deficit model in self-regulation, distress tolerance and interpersonal skills, believed to arise from transaction between highly sensitive individuals and environments invalidating of their vulnerabilities [54-56]. In this view, incorporating the strategy of validation with the concept of dialectics, DBT focuses on skills acquisition and behavioural shaping to enable patients to become more mindful and to manage their emotions and relationships more effectively. Therein lies the mechanism of change.

Rooted in attachment and cognitive theory, MBT proposes a borderline pathology model based on mentalization deficit, reflected in inability to comprehend own and others' states of mind [57,58]. Instability in emotions and relationships is claimed to develop in constitutionally vulnerable

individuals [59] subjected to early trauma, neglect and inadequate mirroring of emotions by the caregiver [60]. Thus the aim of MBT is to foster the capacity to mentalize in the context of attachment relationships, which constitutes the essence of the mechanism of change. Therapy-induced neural recovery from BPD is theorized to be mediated by enhanced control of neuropsychological systems behind the organization of interpersonal relationships [58].

2.2) Pharmacotherapy for BPD

Despite overwhelming number of drug efficacy studies for BPD, due to methodological issues in the evidence base, pharmacotherapy remains off-label with no Food and Drug Administration (FDA) nor European Medicines Agency (EMA) approved medications for the disorder. Nevertheless, the official treatment guidelines state that pharmacotherapy is an important adjunct used to treat well defined target symptoms, which tend to fall within three behavioural dimensions, namely affective dysregulation, impulsive behavioural dyscontrol, and cognitive perceptual distortion [61,62]. A recent review supported the efficacy of SSRIs, in particular fluoxetine for impulsivity and affective symptoms; mood stabilizers among which valproate, topiramate, and lamotrigine demonstrated efficacy for affective symptoms related to anger and impulsive aggression; olanzapine was the most efficacious among second generation antipsychotics in targeting aggressiveness, affective and cognitive-perceptual symptoms [63]. Furthermore, recent efficacy studies point to novel drugs, such as opioid antagonist [64,65], clonidine [66,67], omega- 3 fatty acids [68-70], and oxytocin [71-73] in reducing affective instability, impulsivity, self - injuries, and dissociative symptoms. Fundamentally, the abundance of options with poorly specified benefits have encouraged polypharmacy, which sometimes leads to undesirable side effects [74].

While traditional pharmacotherapies for BPD target primarily the serotonergic and dopaminergic systems subserving domains of impulsive aggression and affective dysregulation, symptoms associated with interpersonal problems, such as chronic feelings of emptiness, identity disturbance and abandonment seem unresponsive to available pharmacotherapies [75]. The need to develop neurobiologically informed specific medication for these symptoms was encouraged by the theory of altered regulation within the OXT system as the underlying mechanism of interpersonal disturbances in BPD [76]. To date, studies involving healthy and clinical subjects have implicated the OXT system in certain abnormalities in behavioural mechanism closely related to interpersonal disturbances, hence supporting the therapeutic potential of OXT for this domain of pathology. A conceptual framework of mechanisms modulated by OXT was developed including the following: the brain silence network of interpersonal hypersensitivity; the affect regulation circuit regulating top-down processes; the mesolimbic circuit mediating social reward; and brain regions mediating

cognitive and emotional empathy [77]. It is further claimed that the role of OXT may not be specific to borderline pathology, but rather a host of psychiatric conditions were parent-child attachment have been disrupted [78,79]. Whilst evidence for prosocial effects of this neuropeptide in healthy and clinical subjects appear promising, conclusions with regard to BPD are hampered by insufficient research and methodological issues. A recent review of 5 clinical trials of intranasal OXT effects on social cognition in BPD provided conflicting results reflected in attenuated emotional responses to stress as well as worsened interpersonal anxiety and decreased cooperative behaviour [80]. Thus, further research is warranted to reconcile mixed results and to answer the remaining questions on the use of OXT in BPD treatment.

3) Review of fMRI studies on treatment-induced brain plasticity

While clinical benefits of available treatments for BPD have been extensively researched, whether amelioration of symptoms translates into changes in cerebral organization within specific circuits is yet to be established. With this in mind, eight studies of treatment- induced brain plasticity were identified, six focusing on Dialectical Behavioural Therapy (DBT), one on Transference-Focused psychotherapy (TFP), and one on Oxytocin (OXT) (see Table 1). Identified publications were discussed, and important issues summarized for consideration in future research.

Table 1 Neurofunctional changes in the brain associated with treatment models for BPD

	Sample(treatment responders)			Intervention			Study design		Main findings	
Author	**BPD**	**HC**	**CC**	**treatment**	**control**	**Target**	**Task**	**Design**	**Treatment-induced neural changes**	**Conclusions**
Schnell K *et al.* (2007) *ref.* 81	6 (4)	6	--	12-week DBT in-patient program (10 group sessions and 1 individual session per week)	--	Affect regulation	Affective Picture System (IAPS)	5 fMRI scans on days 0, 7, 35, 63 and 91; the DBT program started on day 8	Decrease in HDR to negative stimuli in the left insula, the right anterior cingulate, temporal and posterior cingulate cortices. Reduction of HRF modulation in the left amygdala and both hippocampi.	DBT-induced changes in limbic and cortical regions consistent with psychotherapy effects in other mental disorders.
Goodman M *et al.* (2014) *ref.* 86	11	11	--	12-months of standard-DBT (90 min skills training group and 50–60 min individual session per week with tel coaching as needed).	--	Affective instability	Affective Picture System (IAPS)	2 fMRI scans pre- and post-12-months DBT	Decreased amygdala activation for all pictures, marked in the left hemisphere and during repeated-emotional pictures. Improved amygdala habituation was associated with improved overall emotional regulation (DERS).	DBT targets amygdala hyperactivity as part of the disturbed neural circuitry underlying emotional instability in BPD.

Schmitt R *et al.* (2016) *ref.* 88	32 (17)	24	16	12-week standard inpatient DBT including weekly manualized skills training groups, focused on emotion regulation.	--	Emotion regulation with Re-appraisal strategy	Reappraisal task during the presentation of negative and neutral pictures (IAPS).	2 fMRI scans pre- and post-12-weeks DBT	Reduced insula, OFC, dlPFC and ACC activity during reappraisal. Increased connectivity of ACC to medial and superior frontal gyrus, superior temporal gyrus, and inferior parietal cortices.	Reappraisal may indicate efficient emotion regulation skill mediated by attenuated limbic hyperarousal, greater coupling between limbic and prefrontal and inferior parietal regions.
Winter D *et al.* (2016) *ref.* 91	31 (16)	22	15	12-week of residential DBT (weekly skills training groups on emotion regulation, mindfulness, self-esteem, social skills) and individual treatment 2/week.	TAU	Emotion regulation with Distraction strategy	Distra-ction task during the presentation of negative and neutral pictures (IAPS).	2 fMRI scans pre- and post-12-weeks DBT	Decreased right inferior parietal lobe/supramarginal gyrus activity during distraction, which was correlated with self-reported borderline symptom severity improvement. Decreased right perigenual ACC activity while viewing negative pictures	DBT-induced changes in neural activity associated with distraction during emotion processing point to lower emotional susceptibility after amelioration of BPD symptoms.
Niedtfeld I *et al.* (2017) *ref.* 92	28	23	15	12-week standard inpatient DBT (2.5 h per week of individual therapy, and skills training group).	TAU	Affect-regulating function of pain in BPD	Task was to watch pictures (IAPS), combined with temperatur e stimuli.	2 fMRI scans pre- and post-12-weeks DBT	Pain as a means of affect regulation in BPD, indicated by increased amygdala coupling. Reduced amygdala deactivation in response to pain and reduced connectivity between left amygdala and dlACC.	It was demonstrated that pain-mediated affect regulation can be normalized with a successful DBT.
Ruocco AC *et al.* (2016) *ref.* 94	29 (18)	--	--	7-month stand residential DBT (1 h/week individ. session and 2 h/week group therapy on coping strategies and validation.	--	Impulse control, Self -harm	Scarbo-rough Non-Affective Go/No-go Task	2 fNIRS scans pre- and post-7-months of DBT	Treatment response associated with lower activity in dlPFC before RBT with the greatest post- DBT increases in activity recorder in these regions. Treatment attrition associated with greater pre-DBT activity in mPFC and right inferior frontal gyrus.	Treatment response and attrition may be predicted from pre-treatment patterns of PFC activation.
Perez DL *et al.* (2016) *ref.* 98	10	--	--	TFP (average number of sessions attended=76.60 , SD=8.28). TFP consisted of twice weekly individual, 50-minute sessions.	--	Emotional and behavioral regulation	Disorder-specific emotion-nal linguistic *go /no-go* fMRI paradigm	2 fMRI scans pre- and post-design (average scan interval=12 .1 months; range=10–14 months)	Increased activity in dorsal ACC, dlPFC, and frontopolar cortex together with decreased activity in vlPFC and hippocampus. Pre-TFP hypoactivation in r/dACC predicted improvement in constraint, and left mOFC/ventral striatum hypoactivation in affective lability.	Amelioration in self-regulation deficit under TFP is mediated by neural alterations in frontolimbic circuitry.
Bertsch K *et al.* (2013) *ref.* 100	19	21 20	19	26 IU of intranasal OXT 45 min prior to scans	Pla-cebo	Emotion regulation	Emotion classificatio n task.	Randomize d placebo-controlled double-blind group design	OXT reduced amygdala activation in response to angry faces, and normalized number and speed of initial fixation changes to the eyes of angry faces.	OXT may reduce anger and aggressive behaviour in BPD by decreasing social threat hypersensitivity.

*The table shows fMRI studies of neural mechanisms mediating post treatment amelioration of BPD symptoms following psychosocial treatments and Oxytocin.

3.1) fMRI studies of DBT-induced brain changes

To date, six fMRI studies have examined neurofunctional changes under DBT in BPD subjects. Two

early pilot studies set out to establish whether DBT- induced improvement in regulation of affective arousal in BPD patients was mediated by alterations in underlying cerebral networks. In the first study [81] six unmedicated female BPD patients matched against six healthy controls were scanned five times before, during and after a 12-week in-patient treatment program while viewing the International Affective Picture System [82]. Functional changes in four treatment responders revealed neural changes in limbic and cortical regions, including decreased activity in ACC, PCC, insula, left amygdala and both hippocampi to aversive stimuli relative to controls. The most striking difference between groups was evident in reduced activation in the caudal ACC in BPD patients. Although the study succeeded in highlighting the role of amygdala normalization consistent with psychotherapy effects in other mental disorders [83-85], it has to be interpreted with caution as the response criteria dividing patients into responders and non-responders were defined by meeting two or three treatment objectives rather than standardized instruments. This limitation was addressed by Goodman [86] who examined the effect of 12-month course of DBT on amygdala activity and overall emotion regulation, as measured by changes in the Difficulties in Emotion Regulation Scale (DERS) [87]. Unmedicated BPD outpatients matched to healthy controls were pre- and post- DBT treatment scanned. They exhibited significant reduction in overall amygdala activation, which was particularly notable in the left hemisphere and during repeated- emotional pictures. Furthermore, attenuated activity in the amygdala to repeated unpleasant pictures was associated with an improvement in overall emotion regulation (DERS). Thus, the notion that DBT targets amygdala hyperactivity in BPD was supported, however, the pilot nature of both studies, a small sample size and limited statistical power render results preliminary. Finally, aforementioned studies did not include a clinical control group and therefore borderline- specific conclusions cannot be made.

Two following studies focused on DBT associated changes in neural correlates of various emotion regulation strategies and related symptom characteristics. Schmitt *et al*. [88] set out to investigate the effect of a 12-week inpatient DBT program on neural correlates of reappraisal in 32 female DBT patients, compared to 24 healthy control participants, and a clinical control group of 16 BPD patients. Participants received either constant medication (54.2%) or no medication (45.8%) during the study period. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) [89] was used to determine treatment response, and 17 identified responders were compared against the clinical control group. Participants were scanned before and after a DBT program while performing a reappraisal task [90]. The study revealed post- treatment reduction in the insula and ACC activity, with increased connectivity of ACC to medial and superior frontal gyrus, superior temporal gyrus and inferior parietal cortices. Thus, treatment response was associated with attenuated activation in the amygdala, ACC, OFC, and dlPFC, with elevated connectivity within a limbic-prefrontal network during the reappraisal of negative stimuli after DBT. Similarly, Winter *et al*. [91] investigated whether neural correlates of distraction might change with a successful DBT. It was hypothesized

that after the treatment patients would exhibit stronger use of a fronto-parietal emotion regulation network and attenuated limbic hyper-reactivity during a distraction task. 31 BPD patients under constant medication at each fMRI measurement were scanned before and after a 12- week residential DBT-based treatment during a distraction task. They were compared to 15 BPD control patients, either under non-DBT-based treatment or no treatment at all, and 22 healthy participants. When compared to both control groups, 16 DBT responders exhibited attenuated activity in the right inferior parietal lobe/supramarginal gyrus during distraction from negative rather than neutral stimuli, which was correlated with improvement in self-reported borderline symptom severity (ZAN-BPD). They also evidenced reduction in the right perigenual ACC activity and increased activity in these regions during distraction in the context of aversive stimuli. Thus, post- DBT changes in neural activity associated with distraction were interpreted as a shift from emotional to more cognitive processing during viewing aversive stimuli, which suggests a lower emotional susceptibility during distraction after successful DBT. Even if the percentage of medicated individuals did not differ between BPD groups, they received combinations of drug subtypes making it impossible to isolate the effect of a single agent. As previously established, drugs may attenuate emotional responses in BPD patients [47].

New insight into the effect of DBT on pain perception and neural processing of pain in BPD was provided by Niedtfeld *et al.* [92], who investigated whether neural mechanism driving the role of pain in emotion regulation in BPD could be normalized under the treatment. Changes in pain threshold or appraisal of pain under 12-week inpatient DBT program were examined in 28 female BPD patients, compared to 15 patients with treatment as usual, and 23 healthy control subjects. They were fMRI scanned before and after treatment, pairing the presentation of picture stimuli eliciting negative emotions (IAPS, EPS) with thermal stimuli inducing heat pain, in order to establish the role of pain in emotion regulation. Treatment response was assessed resulting in 13 responders and 15 non-responders using reliable change index [93]. Results revealed pretreatment amygdala deactivation in response to painful stimuli, and altered connectivity between left amygdala and dorsal ACC in BPD patients. Following DBT these changes reduced as compared with patients under treatment as usual with no observed differences in pain thresholds between patient groups. Although the study succeeded in demonstrating that neural pain processing in BPD tended to normalize with DBT, presumably due to treatment-induced increased functional emotion regulation, firm conclusions cannot be drawn. The study is limited by low statistical power, flawed by employing self- selection process in assigning patients to DBT treatment, and the use self-rating scale to measure pain.

While aforementioned studies focused on neural changes mediating amelioration in affective regulation, one study examined pre-and- post DBT activation in PFC during impulse control in self-

harming BPD patients as a potential predictor of treatment outcomes [94]. Since DBT targets deficits in response inhibition considered to underlie self-harm [95,96], it was investigated whether patterns of activation in neural correlates of target deficits may isolate markers of treatment response and attrition. In this view, 29 actively self-harming BPD patients (90.30% females) completed functional near-infrared spectroscopy (fNIRS) neuroimaging procedures prior to and after 7 months of DBT. The Scarborough Non-Affective Go/No-go Task was used to measure motor inhibitory control, known to probe bilateral medial and inferior frontal gyri during response inhibition [97]. Patients who benefited most from the treatment in terms of reduced incidence of self- harm exhibited attenuated levels of activity in dlPFC before therapy, and were characterized by the highest increases in activity in this region after 7 months of treatment. In addition, increases in the right dlPFC activity was associated with lesser incidence of self-harm, even when improvements in BPD symptoms severity, depression and mania were accounted for. Five patients who did not complete the treatment demonstrated greater pre-treatment activation in the medial PFC and right inferior frontal gyrus compared to treatment-completers, which is likely to reflect a lesser recruitment by the PFC of inhibitory control processes. Thus, the study put forward the notion that pre-treatment patterns of neural activity in areas of the PFC mediating impulse control in BPD patients may be associated with treatment responses to DBT and attrition from therapy.

3.2) fMRI study of TFP-induced brain changes

With regard to psychodynamically oriented therapy, only one pilot study examined TFP-induced alterations in frontolimbic neural activation behind symptom amelioration in domains of constraint, affective liability and aggression, as well as predictors of treatment response in BPD [98]. Ten diagnosed females were pre- and post-treatment scanned 10-14 months apart while performing emotional-linguistic go/no-go paradigm [99]. Some of them had comorbid panic disorder, phobia, generalized anxiety disorder, alcohol and substance abuse, as well as diagnoses of personality disorders. Moreover, five patients reported to be on psychotropic medication during the study period. Results revealed post -TFP relative increase in activation within dorsal prefrontal areas (dorsal anterior cingulate, dorsolateral prefrontal, and frontopolar cortices), and relative decrease in activation within ventrolateral PFC and the hippocampus. Furthermore, amelioration in constraint and affective lability were positively correlated with relative increase in activation of the left dorsal ACC and left posterior-medial OFC/ventral striatum activation, respectively. In addition, improvement in affective liability was negatively correlated with activation in the right amygdala/parahippocampal. With regard to predictors of treatment outcomes, pre- TFP hypoactivation in the right dorsal ACC was associated with post- treatment improvements in constraint, whereas pre-treatment hypoactivation in the left posterior-medial OFC/ventral striatum

hypoactivation predicted amelioration in affective lability. These preliminary findings provided the first account of alterations in frontolimbic circuitry induced by a psychodynamically oriented psychotherapy.

3.3) fMRI studies of oxytocin-induced brain changes

Given that OXT was previously shown to optimize reflexive processing of social cues and modulate the salience of social information by attenuating amygdala activity, one study investigated its effect on facial threat processing in BPD, typically characterized by hypersensitivity and the tendency to disambiguate neutral into angry expressions [100]. Patterns of amygdala activity in response to angry and fearful compared with happy facial expressions were scanned in 40 nonmedicated BPD female patients and 41 healthy women during emotion classification task 45 minutes after intranasal administration of 26 IU of oxytocin or placebo. Eye tracking combined with fMRI scans revealed post-OXT reduction in posterior amygdala hyperactivation associated with reduced attentional bias toward socially threatening cues in BPD females. The strongest effects were observed in the posterior part of the amygdala, presumably corresponding to the basal nucleus involved in assigning salience to negative facial expressions and in redirecting attention toward socially pertinent locations within visual field [101,102]. Thus, the study shed initial light on down-regulation of social salience by intranasal administration of OXT in BPD, which may help to reduce stress reactivity and improve threat-driven reactive aggression in the disorder. However, as no clinical control group was included in the study, caution must be exercised while drawing borderline- specific conclusions.

Discussion

First and foremost, preliminary evidence supports that DBT achieves its therapeutic effect on emotion regulation through changes in limbic and cortical networks [81, 94], which further advances the thesis that the treatment targets frontolimbic imbalances as part of the disturbed circuitry [10]. Patterns of decreased activity in ACC, PCC, insula, left amygdala and in both hippocampi to aversive stimuli supported the role of amygdala normalization, which is consistent with psychotherapy effects in other mental disorders [82-84]. Importantly, reduction in the caudal ACC in the target group points to a more efficient use of cognitive strategies to attenuate adverse feelings [11], hence may indicate biological underpinnings behind therapeutic processes of affective dysregulation. Treatment effects were particularly notable in the left hemisphere, which was associated with an improvement in overall emotion regulation (DERS).

Consistent with skills deficit model of BPD, gathered evidence supports that acquisition of affective control strategies under DBT translates into alteration within underlying neural substrates of emotion regulation. Although skills training is the main focus of the therapy, only two studies have

investigated pre-and-post DBT alteration in underlying brain activity pattern. Schmitt *et al*. [88] demonstrated that improved cognitive reappraisal after 12-week inpatient program was associated with dampened insula and ACC activity, coupled with enhanced connectivity of the latter to medial and superior frontal gyrus, superior temporal gyrus, and inferior parietal cortices. Furthermore, post-treatment increase in dorsal ACC activity during exposure to negative stimuli was associated with improvement self-reported BPD symptoms, thus elucidating possible neural marker of improved emotion control. These findings build on prior knowledge of reduced prefrontal-limbic connectivity and the role of prefrontal limbic regions in successful emotion control in BPD [18]. Thus, rethinking feelings mediated by quieting of amygdala, ACC, OFC, and dlPFC, as well as enhanced limbic-prefrontal network connectivity, appears to be effective in reducing BPD symptomatology.

In addition, successful DBT may trigger adaptive changes in neural correlates of distraction (91). This was reflected in post-treatment reduction in the right perigenual ACC activity and increased activity in these regions during a distraction task in the context of aversive stimuli. Furthermore, attenuated activity in the right inferior parietal lobe/supramarginal gyrus during distraction from negative stimuli was found to be correlated with improvement in self-reported borderline symptoms. These alterations in activity patterns indicate a shift from emotional to more cognitive processing in the presence of aversive stimuli, which may suggest a lower emotional susceptibility after successful DBT. Interestingly, reduced limbic hyper-reactivity during distraction not associated with BPD symptom improvement supports the notion of distraction being an automatized and overlearned emotion regulation strategy [103], which attenuates limbic reactivity to aversive stimuli independent of symptom severity. Although results complement prior findings of elevated insular and limbic responding associated with disturbed fronto-parietal, inhibitory functioning in BPD patients during distraction from negative stimuli, caution must be exercised while interpreting both studies as patients were not medication- free.

Initial evidence exists to suggest that providing adaptive emotion regulation techniques under DBT may reduce the soothing effect of pain on emotional arousal at the neural level [92]. While pre-treatment application of painful stimuli to BPD patients triggered amygdala deactivation together with altered connectivity between left amygdala and dlPFC, thus confirming the role of pain in emotion regulation, these activity patterns tended to normalize with treatment. Also, the thesis that DBT targets deficits in response inhibition underlying self-harm was supported by evidence of post-treatment increase in right dlPFC activity associated with reduction in self-harm [94]. In addition, treatment responders evidenced lower pre- treatment levels of neural activation in the dlPFC, whereas treatment attrition was predicted by elevated medial PFC and right inferior frontal gyrus activity. While PFC has been strongly linked to response inhibition, it subserves this cognitive

ability as a part of a larger cerebral network [23], hence focusing on this region only may constitute a major limitation of this study.

Strikingly, there is only one report of alterations in frontolimbic circuitry under TFP, which suggests that the mechanism by which the treatment achieves change involves increased activity within dorsal prefrontal areas (dorsal ACC, dlPFC, and frontopolar cortices), and decreased ventrolateral PFC and hippocampus activation [95]. In addition, pre- TFP hypoactivation in the right dorsal ACC predicted post- treatment improvements in constraint, whereas pre-treatment hypoactivation in the left posterior-medial OFC/ventral striatum hypoactivation was associated with amelioration in affective lability. Finally, one study supports that the therapeutic action of OXT occurs via reducing amygdala activation, which optimizes reflexive processing of social cues and modulates the salience of social information [100]. The strongest effects were observed in the posterior part of the amygdala, presumably correspond to the basal nucleus involved in assigning salience to negative facial expressions and in redirecting attention toward socially pertinent locations within visual field [101,102]. However, as no clinical group was included in the study, caution must be exercised while drawing borderline- specific conclusions.

Conclusion

The past decade of neuroimaging research has helped to elucidate some key processes that BPD treatments entail at brain level to achieve therapeutic change. Evidence suggests that successful DBT alters neural underpinnings of emotion regulation, TFP downregulates key neural circuits of impulsivity, and OXT attenuates amygdala activation, and therefore optimizes reflexive processing of social information. These findings allow to speculate that different therapeutic models are unlikely to have a specific neural mechanism of action. Taken together, evidence shows that treatment-induced neural recovery from BPD occurs via downregulation of neuronal activity within limbic regions, including the insula and amygdala, together with differential employment of prefrontal areas, mainly OFC, ACC and dlPFC, as well as enhanced functional connectivity between limbic and prefrontal regions. Although preliminary evidence is limited by the pilot nature of studies, low power, small sample size and generalizability issues, statistically significant results warrant future efforts to disentangle key neural circuits behind treatment processes to refine strategies for specific symptoms. Understanding how various treatments achieve their therapeutic effects on neural functioning will not only advance the empirical status of evidence- based treatments, but might also contribute to resolving some of the existing controversies over BPD treatment.

Future perspective

Future studies on treatment- induced bran plasticity in BPD should disentangle key neural circuits underlying variety of treatments for which evidence of efficacy has been demonstrated:

- Apart from DBT, brain changes under other established evidence based treatment should be examined, namely Mentalization- Based treatment (MBT), Transference- Focus psychotherapy (TFP), Schema- Focused therapy (SFT) and systems training for emotional predictability and problem solving (STEPPS)
- Further research is warranted to reconcile mixed results, and to answer the remaining questions on the use of OXT in BPD treatment.
- Novel drugs such as opioid antagonist, clonidine, omega- 3 fatty acids, have demonstrated efficacy in reducing affective instability, impulsivity, self - injuries, and dissociative symptoms and therefore should be the focus of future research on treatment- induced brain plasticity.

Executive Summary

1. Introduction

- Although neural substrates of symptoms expression in Borderline Personality Disorder (BPD) have been studied extensively, neural mechanisms of post treatment amelioration of symptoms remain poorly understood.
- This review sheds a critical light on all here-to-date fMRI findings of brain changes in BPD patients following a treatment with psychotherapy or drugs.
- Publications until October 2017 were selected through systematic literature search or identified manually by searching reference lists of selected articles.

2. Review of fMRI studies

- Eight studies of treatment- induced brain plasticity were identified, six focusing on Dialectical Behavioural Therapy (DBT), one on Transference-Focused psychotherapy (TFP), and one on Oxytocin (OXT).

2.1. fMRI studies of DBT effects

- Preliminary evidence suggests that neural underpinnings of emotion regulation in BPD may change under DBT.
- This was reflected in downregulation of neuronal activity within limbic regions, including the insula and amygdala, together with differential employment of prefrontal areas, mainly OFC, ACC and dlPFC, as well as enhanced functional connectivity between limbic and prefrontal regions

2.2. fMRI study of TFP effects

- TFP induced elevated dorsal prefrontal activity during go/no-go paradigm, which might indicate key neural circuits of impulsivity.

2.3. fMRI studies of oxytocin effects

- Oxytonergic effects on facial threat processing was reflected in reduced activation of the amygdala, thereby optimizing reflexive processing of social cues and modulating the salience of social information.

3. Discussion

- Preliminary evidence suggests that neural underpinnings of emotion regulation in BPD may change under DBT
- Evidence, albeit limited by the pilot nature of studies, low power, small sample size and generalizability issues, warrant future efforts to disentangle key neural circuits underlying treatment processes.
- Knowing how various treatments achieve their therapeutic effects on the level of brain reorganization will refine treatment strategies, and may resolve existing controversies over BPD treatment.

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